

<b>Protocol Title:</b>	MB02-C-02-17: STELLA – A Randomized, Multicenter, Multinational, Double-Blind Study to Assess the Efficacy and Safety of MB02 (Bevacizumab Biosimilar Drug) Versus Avastin® in Combination With Carboplatin and Paclitaxel for the Treatment of Subjects With Stage IIIB/IV Non-squamous Non-Small Cell Lung Cancer (NSCLC).
<b>NCT Number:</b>	NCT03296163
<b>SAP version date:</b>	Version 2.0, 03 Apr 2020



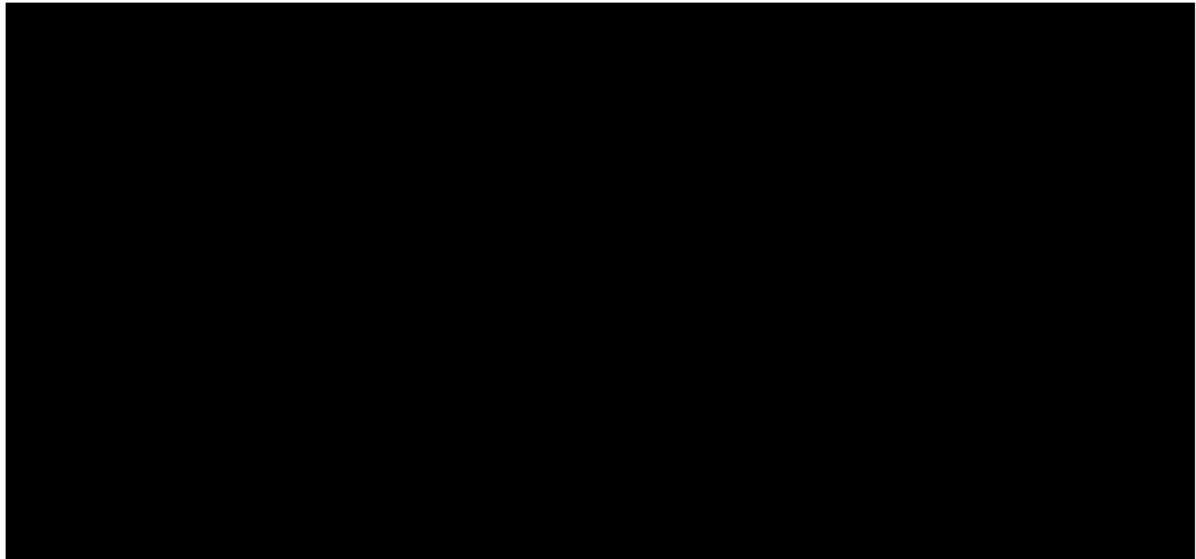
<b>Sponsor Name:</b>	mAbxience
<b>Protocol Number and Title:</b>	MB02-C-02-17: STELLA - A Randomized, Multicenter, Multinational, Double-Blind Study to Assess the Efficacy and Safety of MB02 (Bevacizumab Biosimilar Drug) Versus Avastin® in Combination With Carboplatin and Paclitaxel for the Treatment of Subjects With Stage IIIB/IV Non-squamous Non-Small Cell Lung Cancer (NSCLC)
<b>Protocol Version and Date:</b>	Version 1.0 of 04 August 2017
<b>Phase</b>	3
<b>Protocol Amendment</b>	Amendment 1, Version 3.0, 03 December 2018
<b>Syneos Health Project Code:</b>	1009920B
<b>Author(s):</b>	[Redacted] Principal Statistician
<b>SAP Version:</b>	2.0
<b>SAP Version Date:</b>	03-APR-2020

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## Revision History



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## 1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ADA	Anti-Drug Antibodies
ADR	Adverse Drug Reaction
ALT	Alanine Transaminase
aPTT	activated Partial Thromboplastin Time
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
BDRM	Blinded Data Review Meeting
BMI	Body Mass index
BSA	Body Surface Area
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CrCl	Calculated Creatinine Clearance
CRF	Case Report Form
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
CT	Computed Tomography
CV	Coefficient of Variation
DOR	Duration of Overall Response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GPP	Good Pharmacoepidemiology Practice

Abbreviation	Description
ICH	International Conference on Harmonization
HB	Hemoglobin
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
HR	Heart Rate
INR	International Normalized Ratio
IRC	Independent Radiology review Committee
IMP	Investigational Medicinal Product
ITT	Intention To Treat
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MRI	Magnetic Resonance Imaging
N/A	Not Applicable
NA	Not Applicable
NCI	National Cancer Institute
NCRNPD	Non-CR/Non-PD
NCS	Non Clinically Significant
NE	Not Evaluable
NSCLC	Non-Small Cell Lung Cancer
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PASS	Post Authorization Safety Study
PAES	Post Authorization Efficacy Study
PD	Progression of Disease
PFS	Progression Free Survival
PH	Proportional Hazards
PPS	Per Protocol Set
PR	Partial Response
PT	Preferred Term
QC	Quality Control

Abbreviation	Description
QTc	Corrected QT Interval
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
RD	Risk Difference
RMST	Restricted Mean Survival Time
RR	Risk Ratio
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
sd	Standard Deviation
SD	Stable Disease
SE	Standard Error
SI	Standard International System of Units
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
TPR	Time Point Response
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell
WHO	World Health Organization

## **2. PURPOSE**

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

### **2.1. RESPONSIBILITIES**

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

### **2.2. TIMINGS OF ANALYSES**

The primary analysis of safety and efficacy is planned after all subjects have completed the scheduled procedures at Week 18 or terminate early from the study.

Unless otherwise specified, the analysis includes all data collected in the database through the time of the database lock at week 18. A follow-up analysis will be conducted when all subjects complete the final visit of the follow-up phase of the study.



### 3. STUDY OBJECTIVES

#### 3.1. PRIMARY OBJECTIVE

The primary objective of the study is to compare the Objective Response Rate (ORR) of MB02 and EU approved Avastin®, when they are administered in combination with carboplatin and paclitaxel in subjects with Stage IIIB/IV non-squamous NSCLC as assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (January 2009).

#### 3.2. SECONDARY OBJECTIVE(S)

- To evaluate the safety profile of MB02 compared with Avastin® in subjects with Stage IIIB/IV non-squamous Non-Small Cell Lung Cancer (NSCLC) as per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.
- To assess the potential immunogenicity of MB02 compared with Avastin® assessed through determination of antidrug antibodies (ADA).
- To assess Progression-Free Survival (PFS) and Overall Survival (OS) at Week 18 and at Week 52 compared with those of Avastin®.

#### 3.3. BRIEF DESCRIPTION

This is a multicenter, multinational, double-blind, 1:1 randomized, parallel-group, equivalence Phase III study to compare the efficacy and safety of MB02 plus chemotherapy (carboplatin and paclitaxel) versus Avastin® plus chemotherapy (carboplatin and paclitaxel) in 600 subjects with Stage IIIB/IV non-squamous NSCLC. MB02/Avastin® plus chemotherapy will be repeated every 21 days for 6 cycles unless there is evidence of disease progression or intolerance of the study treatment. After 6 cycles, (ie, at the start of Cycle 7), subjects can continue to receive MB02/Avastin® monotherapy treatment every 3 weeks until evidence of disease progression or until unacceptable toxic effects develop.

The study ends at Week 52; no further study assessments will be made after this time. After Week 52, all subjects (including those randomized to Avastin® during the study) will be offered the opportunity to continue receiving biosimilar MB02 monotherapy until disease progression, unacceptable toxicity or death. No further study-related procedures are intended to be performed after Week 52; any assessments after Week 52 should be performed based on the investigator's discretion and according to local standard practice.

Subjects eligible for the current study will be randomized centrally in a 1:1 manner and stratified by sex (male/female), smoking status (smoker/nonsmoker), disease diagnosis (newly diagnosed/recurrent disease) and stage (IIIB/IV). A rationale for the study design is presented in section 7.2 of the study protocol.

Tumor assessments will be performed at intervals of 6 weeks, from Cycle 1 Day 1 until the end of Cycle 6 (ie, 18 weeks after first study drug administration); after Cycle 6, tumor assessments will be performed at intervals of 9 weeks until evidence of disease progression and/or the start of new antitumor treatment, death, or Week

52 (End-of-Study Visit), whichever occurs first. Subjects who withdraw for any reason other than progression of disease (PD) or withdrawal of consent will be followed up every 9 weeks with tumor assessment until PD and/or the start of new antitumor treatment, subject decision, death, or Week 52 (End-of-Study Visit) whichever occurs first. Subjects who withdraw because of PD and/or initiate new antitumor therapy or those who progress during the Follow-up Period will then be followed up for survival at intervals of 12 weeks until death or Week 52 (End-of-Study Visit), whichever occurs first. No further tumor assessment will be required.

The primary endpoint is ORR (ie, CR or PR per RECIST version 1.1) at Week 18; an independent radiology review committee (IRC) will assess the primary efficacy endpoint using CT and/or MRI according to RECIST version 1.1 criteria.

A DSMB will assess the safety data periodically and will recommend to the Sponsor whether to continue, modify or stop the trial. This decision will be based on benefit risk evaluation. Further details of the DSMB are provided in section 9.2 of the study protocol.

If a subject discontinues treatment before Week 52 from study drug administration, he/she will be requested to attend follow-up visits. The following assessments will be made:

- Subjects with no radiological disease progression will be assessed for: tumor evaluation, initiation of other treatments, physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, supine vital signs, concomitant medications, surgeries, procedures, Adverse Events/Serious Adverse Events (AEs/SAEs), concomitant diseases and immunogenicity will be recorded in the electronic case report form (eCRF) at follow-up visits at intervals of 9 weeks up to disease progression, death or Week 52 (End-of-Study Visit).
- Subjects that discontinue treatment with radiological progression and/ or initiate new antitumor therapy will be assessed for: initiation of other treatments, concomitant medications, surgeries, procedures, AEs/SAEs (ongoing and/or related to drug study) and concomitant diseases, all of which will be recorded in the eCRF. Subjects will be followed up for survival at intervals of 3 months ( $\pm 14$  days) until death or Week 52 End-of-Study Visit (documented phone call is acceptable), but no further tumor assessment will be required.

If a subject discontinues MB02/Avastin® treatment before completing 6 cycles of therapy and before the primary endpoint at Week 18, the subject must discontinue study treatment and proceed to the End-of-Treatment visit. If a subject discontinues paclitaxel and carboplatin before completing 6 cycles of therapy and before the primary endpoint at Week 18, the continuation of bevacizumab (MB02 or Avastin®, as allocated) as monotherapy should be justified and discussed with the Sponsor prior to such a change in schedule.



### 3.4. SUBJECT SELECTION

#### 3.4.1. Inclusion Criteria

To be eligible for study entry, subjects must satisfy all of the following criteria:

1. Males and female subjects aged  $\geq 18$  years to  $\leq 80$  years.
2. Signed informed consent must be obtained before initiation of any study-specific procedures or treatment as confirmation of the subject's awareness and willingness to comply with the study requirements.
3. Subjects should have newly diagnosed or recurrent Stage IIIB/IV (defined by seventh edition of the TNM classification for Lung Cancer, 2010) non-squamous NSCLC not amenable to curative intent surgery, and not have received any systemic therapy for advanced disease (exclusion criteria 3 and 4). For subjects with recurrent disease, at least 6 months must have elapsed before randomization from previous adjuvant treatment. For Stage IV disease, malignant pleural or pericardial effusion must be confirmed by cytological examination if the effusion is the only lesion that confirms Stage IV of the disease. In all other cases, the cytological confirmation of effusion is not mandatory.
4. Previous radiation therapy if completed  $>4$  weeks before randomization. Palliative radiotherapy to bone lesions is allowed if completed  $>2$  weeks of randomization.
5. Subjects must have at least 1 unidimensional measurable lesion per RECIST version 1.1 (assessed locally).
6. Subjects must have an ECOG performance status  $\leq 1$  at Screening.
7. Subjects must have adequate hepatic, renal and hematologic function defined as:
  - Hepatic function: bilirubin level  $<1.5$  Upper Limit of Normal (ULN), alanine transaminase (ALT) and aspartate transaminase (AST) levels  $<2.5 \times \text{ULN}$ .
  - Renal function: serum creatinine level  $<1.5 \times \text{ULN}$ , calculated creatinine clearance (CrCl)  $>50$  mL/min (Cockcroft-Gault formula), urine protein to creatinine ratio  $<1$ . Subjects with urine protein-to-creatinine ratio  $>1$  may be enrolled if they have  $<1$  g of protein in 24-hour urine collection.
  - Hematological function: Absolute neutrophil count  $>1.5 \times 10^9$  /L; platelets  $>100 \times 10^9$  /L, hemoglobin (Hb)  $>9$  g/dL.
  - Adequate coagulation parameters such as: INR  $\leq 2.0$  and activated Partial Thromboplastin Time (aPTT)  $\leq 1.5 \times \text{ULN}$  within 7 days prior to randomization for subjects not receiving anticoagulation therapy.

8. Eligible subjects must have a systolic blood pressure of  $\leq 140$  mm Hg and a diastolic blood pressure of  $\leq 90$  mm Hg at screening.
9. Women of childbearing potential, and their partners, must agree to adhere to pregnancy prevention methods throughout the duration of the study (including the Follow-up visits, where applicable). Women of childbearing potential are defined as those who are not surgically sterile (did not undergo bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) and not postmenopausal.

Subjects and their partners must agree to use a highly effective method of contraception, to avoid women becoming pregnant throughout the course of the study. Medically acceptable forms of birth control can include the following, with approval of the treating physician:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, sexual abstinence.
10. Non fertile women can be included, that is, those who are physiologically incapable of becoming pregnant, because of:
    - Hysterectomy.
    - Bilateral oophorectomy (ovariectomy).
    - Bilateral tubal ligation or,
    - Postmenopausal women defined as:

Subjects not using Hormone Replacement Therapy (HRT) and who have experienced total cessation of menses for  $\geq 1$  year and be greater than 45 years of age, objective response (OR), in questionable cases, have a follicle stimulating hormone  $>40$  mIU/mL and an estradiol value  $<40$  pg/mL ( $<140$  pmol/L).

Subjects must discontinue HRT before study enrolment because of the potential for inhibition of cytochrome enzymes that metabolize estrogens and progestins. For most forms of HRT, at least 2 to 4 weeks must elapse between the cessation of HRT and determination of menopausal status; the length of this interval depends on the type and dosage of HRT.

If a female subject is determined not to be postmenopausal, that subject must use adequate contraception, as defined immediately above (inclusion 8).

### 3.4.2. Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria are applicable:

1. Inability to comply with protocol procedures.
2. Participation in another clinical trial or treatment with another investigational agent within 4 weeks or 5 half-lives of investigational agent before randomization, whichever is longer.
3. Subjects previously treated with monoclonal antibodies or small molecule inhibitors against Vascular Endothelial Growth Factor (VEGF) or VEGF receptors, including Avastin®.
4. Subjects who have received previous chemotherapy, immunotherapy, targeted therapy, or biological therapy for their lung cancer. Note: Adjuvant and neo-adjuvant therapy are permitted (see: inclusion criterion 3).
5. Subjects who have known malignant central nervous system disease, with the exception of subjects with treated brain metastases who have completed treatment (radiation, surgery or stereotactic surgery) and have not received steroids for at least 4 weeks before randomization. Subjects with central nervous system metastases treated by neurosurgical resection or brain biopsy performed within 8 weeks before randomization will be excluded. Subjects with known or history of brain metastases must undergo brain imaging during screening.
6. Current or recent (within 10 days of the first dose of study treatment) use of aspirin (at least 325 mg/day) or other nonsteroidal anti-inflammatory drugs with antiplatelet activity or treatment with dipyridamole (Persantine®), ticlopidine (Ticlid®), clopidogrel (Plavix®), or cilostazol (Pletal®).
7. Current or recent (within 5 days) use of therapeutic anticoagulation or use of thrombolytic agent. Prophylactic use of low molecular weight heparin is allowed.
8. Subjects with an International Normalized Ratio (INR) >2, unless receiving active anticoagulation treatment, will be excluded.
9. Subjects who have a diagnosis of small cell carcinoma of the lung or squamous cell carcinoma of the lung. Mixed tumors should be categorized according to the predominant histology. If small cell elements are present, the subject will be excluded.



10. Subjects with known tumors that harbor activating epidermal growth factor receptor and anaplastic lymphoma receptor tyrosine kinase (assessed locally).
11. Subjects who have a history of hypersensitivity to the active substance (bevacizumab, carboplatin, and/or paclitaxel) or any of the excipients (such as trehalose dehydrate, sodium phosphate, or polysorbate 20).
12. Subjects with known active viral infection, including but not limited to: hepatitis B, hepatitis C, or Human Immunodeficiency Virus (HIV).
13. Subjects who are pregnant or breastfeeding. Women of child-bearing potential must have a negative pregnancy test at Screening.
14. Subjects with previous major surgery, open biopsy, open pleurodesis, or significant traumatic injury within 4 weeks before randomization or those anticipated to require major surgery during the study.
15. Subjects who have had a core biopsy taken or have had another minor surgical procedure, excluding placement of vascular access device, closed pleurodesis, thoracentesis, and mediastinoscopy, within 1 week of randomization.
16. Subjects with a history of abdominal fistula, Gastrointestinal (GI) perforation, intra-abdominal abscess within 6 months of randomization.
17. Subjects with a nonhealing wound, active ulcer, or untreated bone fracture.
18. Subjects with previous history of hypertensive crisis or hypertensive encephalopathy.
19. Subjects with New York Heart Association Grade II or greater congestive heart failure, or angina, myocardial infarction within 6 months before randomization; symptomatic arrhythmia or serious cardiac arrhythmia requiring medication; abnormal left ventricular ejection fraction < 50% assessed by ultrasound or multigated acquisition scan.
20. Subjects with a previous malignancy within 3 years of randomization (other than superficial basal cell and superficial squamous (skin) cell carcinoma, or carcinoma *in situ* of the uterine cervix, bladder, or prostate).
21. Subjects with history of a significant vascular event within 6 months before randomization (including, but not limited to myocardial infarction and stroke or transient ischemic attack).

22. Subjects with known bleeding diathesis or significant coagulopathy defined as a bleeding event grade  $\geq 2$  within 3 months before randomization.
23. Subjects with history of grade  $\geq 2$  hemoptysis within 6 months before randomization ( $\geq 0.5$  teaspoons of bright red blood per event).
24. Subjects with a tumor(s) invading or compressing major blood vessels.

Subjects who discontinue from the study prematurely after randomization will not be replaced. Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the electronic case report form (eCRF).

Every attempt will be made to conduct the assessments scheduled for the End-of-Study Visit in any subject that discontinues from the study. The aim is to record data in the same way for discontinued subjects as for subjects who completed the study.

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's file.

The Sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning MB02 or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

### 3.5. DETERMINATION OF SAMPLE SIZE

Based on the recommendations of 2 different agencies, 2 different analyses will be performed: 1 based on Risk Ratio (FDA) and 1 based on Risk Difference (EMA). Hence, the sample size calculation should ensure that sufficient power is retained on both analyses. No multiplicity correction will be applied.

The determination of equivalence will be based on the Intention to Treat (ITT) set. Per protocol set will be used as a supportive set for evaluating sensitivity of the main analysis.

For additional equivalence criteria on the primary endpoint required by the PMDA a 2-sided 95% CI for risk ratio (RR) and risk difference (RD) will also be provided in the ITT and PP populations.

#### Risk Ratio

The US Food and Drug Administration (FDA) requires a primary endpoint of risk ratio (RR) based on ORR, with an equivalence margin of [0.73, 1.36]. In order to gain an understanding of the clinical effect of the reference treatment, Avastin®, a meta-

analysis has been conducted to ascertain the expected ORR for the reference arm, including the following references: Sandler et al. (N Engl J Med 2006;533:2542-50), Johnson et al. (J Clin Oncol 2004;22:2184-91), Niho et al. (Lung Cancer 2012;76:362-7), Reck et al. (Ann Oncol 2010;21:1804-9), and Zhou et al. (J Clin Oncol 2015;33:2197-204). The results of this meta-analysis, conducted using StatsDirect 3 software, are as follows:

STUDY	Responders	N	ORR	95% CI	Weight (%)
Sandler et al.	133	381	0.349	(0.301, 0.399)	22.2%
Johnson et al.	11	34	0.324	(0.174, 0.505)	15.2%
Niho et al.	71	117	0.607	(0.512, 0.696)	20.1%
Reck et al.	114	351	0.325	(0.276, 0.377)	22.0%
Zhou et al.	74	138	0.536	(0.449, 0.621)	20.5%
Total*	403	1021	0.429	(0.322, 0.539)	100%

Abbreviation: ORR = objective response rate.

\*The random effects meta-analysis uses response rates for the reference product, Avastin® based on intent-to-treat population for all 5 studies. Weights are provided based on the random effects analysis. The corresponding fixed effects analysis provides a pooled proportion = 0.394.

The pooled ORR for the reference product was estimated to be 0.429 (42.9%), using a random effects model for the meta-analysis (ie, individual proportion was weighted by the corresponding study size, accounting for random effects); a random effects meta-analysis is chosen in this case due to a high chance of heterogeneity (Cochran Q = 43.8,  $P < 0.0001$ ,  $I^2 = 90.9\%$ ).

Utilizing a 2-sided 90% CI for the Risk Ratio, a reference proportion of 42.9% for Avastin® and an equivalence margin of (0.73, 1.36), a sample size of 300 subjects per arm (600 total) provides approximately 89% power to show equivalence of MB02 plus chemotherapy with Avastin® plus chemotherapy on a primary endpoint of RR. In addition, approximately 81% power is achieved under the same conditions when a 95% CI is used.

Any subjects who discontinue study treatment prior to the 18-week time point, with no Week 18 tumor response assessment (result missing) will be classed as non-responders in the final analysis of the primary efficacy endpoint.

#### Risk difference

The European Medicines Agency (EMA) requested that the Risk Difference (RD) in ORRs is used as the primary efficacy analysis, using an equivalence margin of (-12%, +12%).



Utilizing a 2-sided 90% CI for the RD, 300 subjects per arm are sufficient to show equivalence of MB02 plus chemotherapy with Avastin® plus chemotherapy on RD with 82% power.

In addition a sample size of 300 subjects per arm (600 total) achieves 91% power to detect a non-inferiority margin difference between MB02 plus chemotherapy and Avastin® plus chemotherapy group proportions of -12.0%. The Avastin® plus chemotherapy proportion is 0.429 (42.9%). The MB02 plus chemotherapy proportion is assumed to be 0.309 (30.9%) under the null hypothesis of inferiority. The power was computed for the case when the actual MB02 plus chemotherapy proportion is 0.429 (42.9%). The test statistic used is the one-sided Score test (Farrington and Manning). The significance level of the test was targeted at 5%.

All sample size calculations are conducted using PASS13 software.

### 3.6. TREATMENT ASSIGNMENT & BLINDING

Subjects (ie, the unique subject identifier [ID] consisting of center ID and subject ID) will be randomly allocated (1:1 ratio) to treatment according to a prespecified blocked randomization scheme. Randomization will be stratified by sex (male/female), smoking status (smoker/nonsmoker), disease diagnosis (newly diagnosed/recurrent disease) and stage (Stage IIIB/Stage IV). For stratification purposes, former smokers will be classified as smokers if they stopped less than 5 years ago and as nonsmokers if they have not smoked for 5 years or more, or have stopped prior to study and cannot provide information on when they stopped smoking.

The randomization list will be prepared by Syneos Health by an independent unblinded randomization statistician. The randomization will be performed using a centralized Interactive Web Response System, Endpoint®.

### 3.7. ADMINISTRATION OF STUDY MEDICATION

In section 7.4.1 of the study protocol the complete information of the study drug administration is available. The investigational products are as follows:

- MB02 (test; bevacizumab biosimilar drug sourced from mAbxience Spain), to be administered as an IV infusion at an intended dose of 15 mg/kg on Day 1 of every 3 week treatment cycle.
- Avastin® (reference; sourced from the EU), to be administered as an IV infusion at an intended dose of 15 mg/kg on Day 1 of every 3 week treatment cycle.

### 3.8. STUDY PROCEDURES AND FLOWCHART

In Section 7.1.1 of the study protocol the complete information of the study procedure is available while the flowchart is presented below:

Tests & Procedures	Screening period	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Additional Cycles <sup>b</sup>	End of Treatment	Additional Follow-up Visits (no disease progression)	Additional Follow-up (disease progression)	Week 52 End of Study Visit
Week (Day) <sup>a</sup>	Days -28 to -1	1 (1)	4 (22)	7 (43)	10 (64)	13 (85)	16 (106)	19 (127) then every 3 weeks	Within 3 weeks of last cycle	Every 9 weeks	Every 3 months	52
Window (Days)		-1/+3	-1/+3	-1/+3	-1/+3	-1/+3	-1/+3	-1/+3	± 5	± 7	± 14	± 7
Written Informed Consent <sup>c</sup>	Before any study procedure: -28 to -1											
Eligibility (inclusion/exclusion criteria)	-7 to -1											
Demography data	-28 to -1											
Medical history/ baseline conditions	-28 to -1											
NSCLC History	-28 to -1											
Randomization <sup>d</sup>	-1 to 1											
Physical examination	-14 to -1	X	X	X	X	X	X	X	X	X		X
ECOG/ performance status	-14 to -1	X	X	X	X	X	X	X	X	X		X
Vital signs, weight and height <sup>e</sup>	-14 to -1	X	X	X	X	X	X	X	X	X		X
Hematology <sup>f</sup>	-7 to -1	X <sup>f</sup>	X	X	X	X	X	X	X			
Blood chemistry <sup>f</sup>	-7 to -1	X <sup>f</sup>	X	X	X	X	X	X	X			
Coagulation <sup>f</sup>	-7 to -1	X <sup>f</sup>	X	X	X	X	X	X	X			
Urinalysis <sup>f</sup>	-14 to -1	X <sup>f</sup>	X	X	X	X	X	X	X			

Tests & Procedures	Screening period	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Additional Cycles <sup>a</sup>	End of Treatment	Additional Follow Up Visits (no disease)	Additional Follow Up (disease progression)	Week 52 End Of Study Visit
Week (Day)*	Days -28 to -1	1 (1)	4 (22)	7 (43)	10 (64)	13 (85)	16 (106)	19 (127) then every 3 weeks	Within 3 weeks of last cycle	Every 9 weeks	Every 3 months	52
Window (Days)		-1/+3	-1/+3	-1/+3	-1/+3	-1/+3	-1/+3	-1/+3	±5	±7	±14	±7
Virology <sup>a</sup>	-14 to -1											
Pregnancy test <sup>a</sup>	-14 to -1	X	X	X	X	X	X	X	X			
12-lead electrocardiogram <sup>l</sup>	-28 to -1			X		X	X		X			X
LVEF measurement <sup>p</sup>	-28 to -1								X			
Brain CT <sup>j</sup>	-28 to -1	If clinically indicated										
Tumor assessment <sup>k</sup>	-28 to -1		X		X		X	X <sup>k</sup>	X	X <sup>k</sup>		X <sup>k</sup>
Serum biomarkers (ADA) <sup>j</sup>		X	X		X			X <sup>l</sup>	X	X <sup>l</sup>		X
Prior and Concomitant medications <sup>m</sup>	-14 to -1	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Surgeries and Procedures <sup>m</sup>	-14 to -1	X	X	X	X	X	X	X	X	X	X	X
Adverse events <sup>n</sup>	-28 to -1	X	X	X	X	X	X	X	X	X	X	X
Drug administration		X	X	X	X	X	X	X				
Initiation of new antitumor therapy recorded <sup>o</sup>										X	X	X
Survival Status <sup>o</sup>		X	X	X	X	X	X	X	X	X	X	X

NSCLC=non-small cell lung cancer; ECOG=Eastern Cooperative Oncology Group; LVEF=left ventricular ejection fraction; CT= computed tomography; ADA=antidrug antibodies;

PD=progression of disease; WOCBP=women of child-bearing potential;

<sup>a</sup> Calculated using the first day of assigned treatment as Day 1 and unless otherwise specified in other footnotes for a specific activity.

<sup>b</sup> Treatment in additional cycles should continue until: PD, unacceptable toxicity, withdrawal of consent, subject decision, lost to follow-up, protocol violation, death, investigator decision, or subject becomes pregnant.

<sup>c</sup> Must have been obtained before any study-related procedures are performed.

<sup>d</sup> Randomization of subjects will take place on the same day (Day 1) or the day before the planned treatment dose administration (Day -1); should an unintended delay occur, the initial cycle of MB02 must start within 4 (-1/+3) days of randomization.

\* Supine Vital signs including blood pressure, pulse rate, respiratory rate and body temperature. Height will be measured at Screening only.

<sup>†</sup> Laboratory assessments will be conducted by a central laboratory and will include hematology (complete blood count including hemoglobin, hematocrit, white blood cell count with 5-part differential, red blood cell count and platelet count), blood chemistry (bicarbonate, calcium, phosphorus, magnesium, albumin, glucose, serum creatinine, total protein, and blood urea nitrogen), liver function tests (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, and total and direct bilirubin), coagulation analysis (international normalized ratio, prothrombin time, partial thromboplastin time and fibrinogen), and urinalysis (microscopy including protein, protein-to-creatinine ratio (Screening only), specific gravity, glucose, and blood). If protein-to-creatinine ratio is  $\geq 1$  at Screening, then 24-hour urine must demonstrate  $< 1$  g of protein in 24 hours. For routine on-study urinalysis assessments, dipstick is sufficient as long as the urine protein result is less than 2+ (urinalysis also acceptable). If dipstick urine protein result is  $\geq 2+$ , 24-hour urine must demonstrate  $< 1$  g of protein in 24 hours. A window timeframe of  $-5/+3$  days will be allowed for laboratory assessments. If screening laboratory assessments are done within 7 days of Cycle 1 Day 1 (first dose), they do not need to be repeated on Day 1. For retreatment (Cycle 2 and on) purposes, local laboratories may be utilized, in addition to the central laboratory.

<sup>‡</sup> Testing for viral infection is not required at screening only to assess whether the status of viral infection (including but not limited to hepatitis B, hepatitis C, and HIV) is known.

<sup>§</sup> Urine or serum as per local requirements; WOCBP only

<sup>§</sup> Electrocardiogram will be performed at Screening, at Cycle 3 (before dosing), Cycle 5 (before dosing), Cycle 6 (Week 18 [ $\pm 1$  week]), End of Treatment Visit, at Week 52 (Cycle 18 predose) and any time if clinically indicated.

<sup>§</sup> Brain CT will be performed only in subjects with known or history of brain metastases or if clinically indicated.

<sup>§</sup> Perform a CT and/or MRI of the chest, upper abdomen, and any other involved regions. Disease status and tumor response will be assessed per RECIST version 1.1 criteria at Screening (within 4 weeks before the first scheduled dose of study drug) and then every 6 weeks ( $\pm 3$  days) from Cycle 1 Day 1 until end of Cycle 6 (Week 18) and, thereafter every 9 weeks ( $\pm 5$  days) until Week 52, PD, start of new treatment, subject decision, or death, whichever occurs first. Week 18 tumor assessments have a 1 week window ( $\pm 1$  week). In addition, tumor assessment should be performed at any time if clinically indicated. Tumor measurement will also be performed during the End-of-Treatment Visit if it was not done within the previous 4 weeks. Every effort will be made to ensure that the same method of assessment used at Screening is used at all subsequent time points. For those patients who discontinue treatment without radiological disease progression, tumor assessment should be performed every 9 weeks ( $\pm 5$  days) until Week 52, PD, start of new treatment, subject decision, or death, whichever occurs first. Once radiological disease progression is documented, subjects are no longer required to undergo additional tumor assessment.

<sup>§</sup> Blood sample for Serum Biomarkers (ADA) determination will be collected at Week 1 (Cycle 1 Predose), at Week 4 (Cycle 2 Predose), at Week 10 (Cycle 4 Predose), at Week 19 (Cycle 7 Predose), at Week 34 (Cycle 12 Predose) and at Week 52 and, at the End of Treatment Visit if an ADA sample has not been collected within the previous 3 weeks. If study treatment should be delayed, ADA sample should also be delayed accordingly. Once patient discontinues treatment, ADA sample will follow specified weeks as scheduled.

<sup>§</sup> Concomitant medications, surgeries and procedures will be collected/reported from signing of informed consent form until 30 days after last cycle administration. Beyond this date, only concomitant medications, surgeries and procedures administered for an AE or SAE considered related to study drugs will be collected/reported.

<sup>§</sup> All AEs and SAEs will be collected/reported from signing of informed consent form until 30 days after last cycle administration. Beyond this date, only AEs and SAEs considered related to study drugs will be collected/reported.

<sup>§</sup> Subjects who discontinue treatment due to disease progression will be followed up every 3 months ( $\pm 14$  days) until start of new antitumor therapy, death, or week 52, whichever occurs first. This follow-up may be performed through a documented phone call. No further tumor assessments will be required.

<sup>§</sup> Left ventricular ejection fraction to be measured by cardiac ultrasound or multigated acquisition scan at Screening Visit and End of Treatment Visit (if not done in previous 6 weeks); left ventricular ejection can also be measured during any treatment cycle, if clinically indicated.



## 4. ENDPOINTS

### 4.1.1. Schedule of Analyses

The main analysis will be performed once the primary endpoint has been achieved, ie, once the last randomized subject has completed the study up to and including Week 18 or early termination, and any tumor review has occurred. A further analysis will be conducted once all subjects have completed/terminated the study (maximum 52 weeks), this efficacy analysis will be aligned with the needs of the FDA, EMA and PMDA.

This main analysis is intended to support regulatory submission procedures. As this analysis consists of the Week 18 primary analysis, there is no inflation of the type I error rate and so no statistical correction is applied.

Note that a DSMB is installed to monitor unblinded safety data during the course of the study. This is described in a separate DSMB Charter.

The week 18 analyses will consist of summary presentations only (tables, but no plots and no listings), based on the following data:

- Subject disposition (table 14.1.1.1)
- Major protocol deviations (table 14.1.2.1)
- Study populations (table 14.1.2.3)
- Demographic and baseline characteristics (table 14.1.3.1.1)
- NSCLC history (tables 14.1.3.2, 14.1.3.3, 14.1.4.2, 14.1.4.3 and 14.1.4.4)
- Prior and concomitant medication (table 14.1.4.1)
- Treatment compliance (tables 14.1.5.1 and 14.1.5.2)
- Primary outcome - objective response rate and ORR (tables 14.2.1.1.1, 14.2.1.1.2, 14.2.1.1.3, 14.2.1.2.1, 14.2.1.2.2, 14.2.1.2.3, 14.2.1.3.1, 14.2.1.3.3 and 14.2.1.3.5)
- Secondary outcomes - progression free survival and overall survival (table 14.2.2.1.1 and 14.2.2.2.1)
- Adverse events (tables 14.3.1.1, 14.3.1.2, 14.3.1.3, 14.3.1.4, 14.3.1.8 and 14.3.1.9)
- Laboratory evaluations (tables 14.3.4.1.1.1, 14.3.4.1.1.2, 14.3.4.1.1.3, 14.3.4.1.2.1, 14.3.4.1.2.2, 14.3.4.1.2.3, 14.3.4.1.3.1.1, 14.3.4.1.3.1.2, 14.3.4.1.3.2, 14.3.4.1.3.3, 14.3.4.1.4.1, 14.3.4.1.4.2 and 14.3.4.1.4.3)
- ECGs (table 14.3.4.3.5)
- Extent of exposure (tables 14.3.4.5.1 and 14.3.4.5.2)
- ECOG/Performance Status (table 14.3.4.6)
- Left ventricular ejection fraction (table 14.3.4.7)

To preserve the blind for blinded study team members, the following approach will be

used:

The main analysis at Week 18 will be carried out by an unblinded study team that is independent to the blinded study team. Upon, and after, the analysis and reporting of the Week 18 unblinded data, the blinded study team will continue to remain blinded.

This main analysis output will comprise summary tables, but no plots or listings.

To prevent accidental unblinding of specific subjects, the following rules will be applied for this analysis:

- For descriptive statistics: min-max lines will be suppressed.
- For frequency tables containing small numbers of subjects in some categories (e.g., trial termination reasons, demographics/baseline characteristics, AEs & SAEs, and labs), the following rules will be programmed in the tables:
  - If there are events in both treatment groups: the full details will be shown in the table, per treatment group. This does not cause any unblinding of specific subjects.
  - If there are events in only one of the groups (either MB02 or Avastin®): this would unblind these subjects. To prevent this, the individual groups will be left blank in the frequency table, and only the "overall total" group will be populated.
- Shift tables: Any responses occurring in a specific shift that align with the above options will also have the corresponding rule applied.

The analysis tables will be checked for potential unblinding details by the independent unblinded statistician prior to delivery to the sponsor.

#### 4.2. PRIMARY EFFICACY ENDPOINT

Objective response rate (ORR): OR will be assigned for subjects if they experience either CR or PR per RECIST v1.1 at Week 18, as assessed by independent review. This assessment will be carried out by an independent radiology review committee (IRC). The ORR at Week 18 will be calculated as the proportion of subjects with OR, and the RR of the ORRs (MB02/Avastin®), and RD of the ORRs (MB02 minus Avastin®) will be used to determine if MB02 is equivalent to Avastin®. Any subjects who discontinue study treatment before Week 18 (result missing) will be classed as non-responders in the final analysis of the primary efficacy endpoint (both for RR and RD analysis). Based on the recommendations of 2 different agencies, both Risk Ratio (FDA) and Risk Difference (EMA) will be analyzed using the ITT, mITT and PP populations.

#### 4.3. SECONDARY EFFICACY ENDPOINTS

##### 4.3.1. Progression Free Survival

PFS will be defined as the time from randomization to subsequent confirmed progression per RECIST version 1.1, or death (whichever occurs first), measured in weeks and months. Analyses will occur at Week 18 and Week 52; at each analysis, all subject data accrued during the study up to this point will be included to inform survival. Thus, at the Week 18 analysis, any subjects with data occurring after Week 18 will be incorporated into the analyses of survival time.

For the calculation of PFS, progression confirmed by either central independent review (up to Week 18) or local review (after Week 18) of the radiological results will be used as events. This primary analysis will be conducted in the ITT, mITT and PP populations.

The following table summarizes the calculation approach for PFS considering the various situations for censoring (Table 1). This table follows the FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2018 (FDA2007).

Table 1 Calculation of PFS Based Results of Local Review

Situation	Date of Progression or Censoring	Outcome
PD (by either local review or by central review)	Date of radiological assessment showing PD	Event
Death during the study before PD	Date of death	Event
No baseline radiological assessments	Date of randomization	Censored
No death or PD	Date of last adequate radiological assessment	Censored
Treatment discontinuation for clinical (no formal tumor assessment) progression	Date of last adequate radiological assessment	Censored
Treatment discontinuation for toxicity or reason other than PD, clinical progression, or death	Date of last adequate radiological assessment	Censored



Situation	Date of Progression or Censoring	Outcome
New anticancer treatment started with PD beforehand	Date of last adequate radiological assessment before start of new anticancer treatment	Censored
Treatment discontinuation for any reason other than confirmed PD or death, and no post-baseline radiological assessments	Date of randomization	Censored

PD = progression of disease

Note: An adequate radiological assessment is one that is evaluable according to RECIST criteria v 1.1. (January 2009) by review of CT and/or MRI results at clinical sites (Klein2003, Collett1994)

#### 4.3.2. Overall Survival

OS will be defined as the time from randomization to subsequent death, measured in weeks and months. Subjects that do not die during the study will be censored at the date of last contact. All available sources in the electronic Case Report Form (eCRF) to determine the last date known to be alive will be used for determination of the censoring date, (e.g. date of last visit, date of last laboratory assessment, date of last adverse event [AE] or date of last imaging, etc). OS analyses will occur at Week 18 and Week 52; at each analysis all subject data accrued during the study up to this point will be included to inform survival. Thus, at the Week 18 analysis, any subjects with data occurring after Week 18 will be incorporated into the analyses of survival time. This analysis will be conducted on the ITT, mITT and PP population.

#### 4.3.3. Duration of Overall Response

The duration of overall response (measured in weeks and months) is the time from date of the first documentation of objective tumor response (CR or PR) to the first documentation of PD, or to death due to any cause in the absence of documented PD.

$DOR = (First\ Date\ of\ Progression\ (or\ death) - Date\ when\ CR/PR\ first\ recorded) + 1$

For subjects with no progression following a response of CR/PR, DOR will be censored at the latest tumor assessment. Death is counted as a progression event.

DOR analyses will occur at Week 52, this analysis will be conducted on the ITT, mITT and PP populations.

#### 4.3.4. Observation Time

The duration of observation time (measured in weeks and months) on the study is the time from date of randomization until final follow-up or death.

$OT = (\text{Last Date of Follow-Up (or death)} - \text{Date of Randomization}) + 1$

For subjects who died they will be censored at their date of death.

OT analyses will occur at Week 52, this analysis will be conducted on the ITT, mITT and PP populations.

#### 4.3.5. Time to Overall Response

The time to overall response (measured in weeks and months) is the time from date of randomization until the date of the first documentation of objective tumor response (CR or PR).

$TTR = (\text{Date when CR/PR first recorded}) - \text{Date of Randomization} + 1$

For subjects with no objective tumor response (CR or PR) TTR will be censored at the latest tumor assessment.

TTR analyses will occur at Week 52, this analysis will be conducted on the ITT, mITT and PP populations.

### 4.4. SAFETY ENDPOINTS

#### 4.4.1. Adverse events

Treatment-emergent AEs (TEAEs) will be listed and summarized using frequencies and percentages. TEAEs will be defined as AEs that occur on or after the date and time of study drug administration. Any AE that first occurs pre-dose but worsens in severity after the first study drug administration will also be considered a TEAE. All AEs will be collected and documented during the course of the study. Subjects will be followed-up until final discharge from the study and any AEs that occur during this time should be reported according to the procedures outlined below:

- All subjects with unresolved AEs at the end of the study, except those who dropped out before randomization or starting active treatment, must be included in a safety follow-up visit to check response of AEs.
- Follow-up can be waived in specific cases after consultation with the sponsor. This permission must be documented per case and retained in the sponsors file.

#### 4.4.2. Laboratory tests

Standard units will be used unless stated otherwise.

Hematology: Complete blood count, including hemoglobin, hematocrit, white blood cell (WBC) count (with 5-part differential), red blood cell count (RBC) and platelet count.

Clinical chemistry: Bicarbonate ( $\text{HCO}_3$ ), calcium, phosphorus, magnesium, albumin, glucose, serum creatinine, total protein, and blood urea nitrogen. Liver function tests: AST, ALT, lactate dehydrogenase, alkaline phosphatase, and total and direct bilirubin.

Coagulation: International normalized ratio, prothrombin time, partial thromboplastin time and fibrinogen.

Urinalysis: Dipstick and microscopy including protein, protein-to-creatinine ratio (screening only, when available), specific gravity, glucose, and blood. Dipstick urinalysis is sufficient as long as the result is less than 2+ (urinalysis is also acceptable).

24-hour urine: If urine dipstick is  $\geq 2+$ , or protein-to-creatinine ratio is  $\geq 1$  at Screening, 24-hour urine must demonstrate  $\leq 1$  g of protein in 24 hours.

Pregnancy (female subjects of child-bearing potential only): Serum or urine  $\beta$  human chorionic gonadotrophin [ $\beta$ -HCG]

Immunogenicity (performed by an external provider): Serum biomarkers (antidrug antibodies) up to 52 weeks after first study drug administration in all randomized subjects. Further details are provided in the laboratory manual. The analysis of such endpoints is not covered in the SAP.

#### 4.4.3. Vital signs

Vital signs: Systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, weight and height will be recorded in metric units (height at Screening only).

#### 4.4.4. Physical examinations

Physical Examinations: The following items and body systems will be assessed: general appearance; eyes, ears, nose and throat, head and neck; chest and lungs; cardiovascular; abdomen; musculoskeletal; lymphatic; dermatologic; neurologic; extremities; endocrine; gynecologic; psychiatric; other. A complete dental examination will also be performed at screening in order to identify any invasive dental procedure.

#### 4.4.5. Eastern Cooperative Oncology Group (ECOG) performance status

Eastern Cooperative Oncology Group (ECOG) performance status will be recorded according to the grades presented in Table 2

Table 2 Summary of Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	ECOG/performance status
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: <http://ecog-acrin.org/resources/ecog-performance-status>. Accessed: 07 April 2017

#### 4.4.6. 12-Lead Electrocardiogram

PR interval, QRS complex duration, QT interval, and QT interval corrected according to Fridericia's formula will be calculated.

#### 4.4.7. Left ventricular ejection

Left ventricular ejection fraction will be measured by cardiac ultrasound or multigated acquisition scan.



## 5. ANALYSIS SETS

### 5.1. SCREENED SET

The Screened Set will include all subjects screened (irrespective of screen failures).

### 5.2. INTENTION TO TREAT (ITT) SET

The ITT analysis set will consist of all randomized subjects. Subjects will be analyzed according to the randomized treatment.

### 5.3. MODIFIED INTENTION TO TREAT (MITT) SET

The mITT analysis set will consist of all randomized subjects who were treated with investigational medicinal product (IMP) and had measurable disease at screening as determined by central radiological review. Subjects will be analyzed according to the randomized treatment.

### 5.4. PER PROTOCOL SET (PPS)

The PPS will consist of all subjects in the mITT set who complete at least the first 6 cycles of IMP and chemotherapy, or who discontinued IMP or chemotherapy after completing at least 4 cycles of IMP and chemotherapy (and withdrew for reasons other than disease progression, death or adverse events); and for whom no major protocol deviations affecting efficacy occur up to and including Week 18.

For protocol deviations refer to Section 5.6.

Subjects from the PPS will be analysed according to the actual treatment received.

### 5.5. SAFETY SET (SAF)

The SAF will consist of all randomized subjects who received at least 1 administration of study drug (IMP). Subjects will be analysed under the actual treatment received.

### 5.6. PROTOCOL DEVIATIONS

Major protocol deviations may include, but are not limited to:

[REDACTED]

Statistical Analysis Plan -  
text

mAbxience Protocol MB02-C02-17

[REDACTED]

Version 2.0

- Concomitant Medications
- Dosing
- Enrollment Criteria
- Informed Consent
- Laboratory
- Non-Compliance
- Regulatory
- Visit Schedule
- Visit/Procedure Required

The final list of major protocol deviations that can affect the primary efficacy analysis will be defined during the blinded data review meeting (BDRM).

## 6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

### 6.1. GENERAL METHODS

All analyses and summaries will be produced using SAS® version 9.3 (or higher).

Unless otherwise specified, summaries will be presented by treatment group and in total.

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (sd), median, first and third quartiles (Q1, Q3), minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency and percentages of subjects.

All relevant subject data will be included in listings.

Unscheduled assessments will not be included in summary tables unless specified otherwise, but will be included in the subject listings.

Early termination assessments will be analysed as having occurred at the next scheduled assessment.

### 6.2. KEY DEFINITIONS

#### 6.2.1. Baseline definition

In general, the last nonmissing valid observation before randomization will serve as the baseline measurement. Assessments occurring on the date of randomization could be included and should occur prior to randomization.

#### 6.2.2. Body Surface Area

The BSA of a subject will be calculated in m<sup>2</sup> using the mosteller method, as  $BSA (m^2) = (\text{height (cm)} \times \text{weight (kg)})^{1/2}$ .

#### 6.2.3. Change from baseline

Absolute change = Post-baseline value - Value at baseline.

Relative change =  $[(\text{Post-baseline value} - \text{Value at baseline}) / \text{Value at baseline}] \times 100$ .

#### 6.2.4. Compliance (study drug)

For IMP and paclitaxel, drug compliance is calculated as the following:

Compliance cycle specific =  $((\text{Actual dose administered [mg]} / (\text{Planned dose [mg]})) * 100\%$

Compliance overall =  $(\text{Sum of all cycle specific (Actual dose administered [mg])} / (\text{Sum of all cycle specific (Planned dose [mg])}) * 100\%$

An additional definition of Compliance overall is given focusing on compliance up to cycle 6 (included). On this definition, values of planned dose [mg] must be nonmissing. In case of missing data for planned dose [mg], the last nonmissing observation will be carried forward.

#### 6.2.5. Day of study termination

Day of study termination = End of study date - Randomization date + 1.

#### 6.2.6. Definition of completion

A subject will be defined as “completed” if s/he remained in study up to end of treatment (see End of study CRF). Termination at a time point prior to this will be considered as discontinuation of the study.

#### 6.2.7. Duration of AE

Duration of AE [days] = Date of stop of AE - Date of start of AE + 1.

#### 6.2.8. Duration of IMP/carboplatin/paclitaxel exposure

Duration of IMP/carboplatin/paclitaxel exposure [days] = Last  
IMP/carboplatin/paclitaxel dose date  
- First IMP/carboplatin/paclitaxel dose date + 1.

#### 6.2.9. Duration of IMP/carboplatin/paclitaxel infusion (within each cycle)

Duration of IMP/carboplatin/paclitaxel infusion [minutes] = (IMP/carboplatin/paclitaxel  
infusion end time - IMP/carboplatin/paclitaxel infusion start time) - (infusion  
interruption time in minutes).



**6.2.10. First IMP/carboplatin/paclitaxel dose date**

The date for which IMP/carboplatin/paclitaxel was first administered.

**6.2.11. Last IMP/carboplatin/paclitaxel dose date**

The date for which IMP/carboplatin/paclitaxel was last administered.

**6.2.12. Fridericia formula for calculation of corrected QC**

$QT_c = QT / ((60/HR)^{0.33})$ . QT is expressed in msec while HR in bpm.

**6.2.13. Planned dose**

The following rules are used for calculating planned doses:

$\text{Paclitaxel planned dose [mg]} = \text{Paclitaxel planned dose [mg/m}^2\text{]} * \text{BSA [m}^2\text{]}$

$\text{Carboplatin planned dose [mg]} = (\text{Carboplatin planned dose [mg/mL x min]} * \text{Volume administered [mL]}) / (\text{Duration of Carboplatin infusion within each cycle [min]})$

$\text{IMP planned dose [mg]} = \text{Intended dose [mg/Kg]} * \text{Weight [Kg]}$

Planned doses are calculated at each applicable cycle.

**6.2.14. Prior/Concomitant medication**

A medication is regarded as “prior” if the stop date of the medication is prior to the randomization date, irrespective of the start date.

A medication is regarded as “concomitant” if it is not “prior” and the start date or stop date of the medication is between the randomization date (included) and the End of study date (included).

A medication is regarded as “concomitant” if ticked as ongoing on the CRF.

**6.2.15. Relationship of IMP/carboplatin/paclitaxel to AE**

An AE is regarded as related if the assessment of causality is possible or probable or very likely/certain for each of the considered study drugs.

**6.2.16. Start Day of previous/concomitant medication**

If medication starts before the randomization date:

Start Day of Medication = Date of start of medication - Date of randomization.

If medication starts at/after the randomization date:

Start Day of Medication = Date of start of medication - Date of randomization + 1.

#### **6.2.17. Study day 1**

The first treatment dose administration.

#### **6.2.18. Time Point Overall Response**

The time point overall response could be CR, PD, PR, SD or NE (see CRF). This is assigned according to RECIST criteria combining target, non-target and new lesions assessment.

#### **6.2.19. Smokers Stratification Definition**

For smoking status (smoker/nonsmoker), for stratification purposes, former smokers will be classified as smokers if they stopped less than 5 years ago and as nonsmokers if they have not smoked for 5 years or more, or have stopped prior to study and cannot provide information on when they stopped smoking.

#### **6.2.20. DSMB Smokers Definition**

Based upon the DSMB recommendation, a definition of 'smokers' will be used in a supportive analysis of efficacy.

The new definition is:

"Never smoker" is a person who smoked less than 100 cigarettes in a lifetime.

Former smoker is a person who has stopped smoking for at least 1 year prior to informed consent, for the DSMB supportive analysis we will have following options:

Non-smoker: never smoked or smoked less than 100 cigarette in a lifetime

Smoker: smoked more than 100 cigarettes in lifetime (despite when quit)

### 6.3. MISSING DATA

All available data will be included in the analyses and will be summarized as far as possible. Unless otherwise specified, there will be no substitution of missing data, i.e., missing data will not be replaced; missing data will be handled as 'missing' in the statistical evaluation.

#### 6.3.1. Safety endpoints

Partial or missing dates of safety data will be imputed according to the most conservative approach.

##### **AEs:**

Unless otherwise specified, missing day will be imputed as the first day of month for all start dates, and as the last day of the month for all stop dates. If the AE start month = month of randomization then the AE start day will be imputed with the day of randomization.

Missing month will be imputed as January for all start dates. However if the AE start year = year of randomization then the month of AE start will be imputed with the month of randomization.

Missing month will be imputed as December for all stop dates. However if the AE stop year = year of end of study then the AE month of stop will be imputed with the month of end of study.

Completely missing start dates for AEs will be imputed as the randomization date.

Completely missing stop dates for AEs will be imputed as the end of study date.

Actual values will be presented in data listings.

##### **Previous/concomitant medications:**

Unless otherwise specified, missing day will be imputed as the first day of month for all start dates, and as the last day of the month for all stop dates.

No stop date will be imputed if the treatment is ongoing.

If the previous/concomitant medication start month and year = month and year of randomization then the previous/concomitant medication start day will be imputed with the day of randomization.

Missing month will be imputed as January for all start dates. However if the previous/concomitant medication start year = year of randomization then the month of previous/concomitant medication start will be imputed with the month of randomization.

Missing month will be imputed as December for all stop dates. However if the previous/concomitant medication stop year = year of end of study then the month of previous/concomitant medication stop will be imputed with the month of end of study.

Completely missing start dates for treatment flagged as ongoing in CRF will be imputed as the randomization date (provided the imputed date is no later than the concomitant medication stop date).

Other completely missing dates will not be imputed.

Other safety endpoints, NSCLC medical history:

For NCSLC medical history start dates:

If only the year is known then impute 02 July.

If month and year are known then impute day as 15.

If day and year are known then month will be imputed as July

#### 6.4. VISIT WINDOWS

##### 6.4.1. Previous visit anchored

No assessments will be anchored on previous visit.

However RECIST v1.1 evaluations will be anchored to cycle 1.

Day is calculated using the first day of assigned treatment as Day 1.

##### 6.4.2. RECIST v 1.1 assessments

RECIST v 1.1 assessments will be performed until PD, start of new treatment, subject decision, lost to follow-up, death or week 52 whichever occurs first. Once radiological disease progression is documented or subject starts a new antitumor therapy, subjects are no longer required to undergo additional tumor assessment.

Name	Week	Windows (days)
Week 6	Week 6 from Cycle 1 Day 1	±3 (days 39 to 45)
Week 12	Week 12 from Cycle 1 Day 1	±3 (days 81 to 87)
Week 18	Week 18 from Cycle 1 Day 1	-7/+14 (days 119 to 140)
Week 27	27 weeks from Cycle 1 Day 1	±5
Week 36	36 weeks from Cycle 1 Day 1	±5
Week 45	45 weeks from Cycle 1 Day 1	±5



End of Treatment	Within 3 weeks of last cycle (only if no assessment performed within the prior 4 weeks)	±5
Follow-up visit 1 (no disease progression)	Every 9 weeks	±5
Follow-up visit 2 (no disease progression)	Every 9 weeks	±5
End of Study	Week 52 (only if no assessment performed within the prior 4 weeks)	±5
Unscheduled		

#### 6.5. POOLING OF CENTRES

Data from all centers will be pooled together.

#### 6.6. SUBGROUPS

The following subgroup analyses will be performed using the stratification covariates of sex (male/female), smoking status (smoker/non-smoker), disease diagnosis (newly diagnosed/recurrent disease) and disease stage (IIIB/IV).

## 7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

### 7.1. SUBJECT DISPOSITION AND WITHDRAWALS

#### 7.1.1. Subject disposition - overall

The number and percentage of subjects fulfilling the following will be summarized by treatment group and overall:

- Screened (overall)
- Screen failure (with reason: Subject Withdrew Consent, Eligibility Criteria Not Met, Adverse Event, Other)
- Total randomized subjects
- Eligible subjects randomized
- Non eligible subjects randomized
- Total randomized subjects treated with IMP
- Total randomized subjects not treated with IMP (with reason: Death, Unacceptable Toxicity, Progressive Disease)
- Completed treatment up to week 18
- Reason not completed treatment up to week 18
- Completed to end of treatment
- Reason not completed to end of treatment
- Completed to end of study
- Reason not completed to end of study

Note that for subjects screened and subject screen failures, the percentage denominator will be the number of screened subjects. For all other calculations, the percentage denominator will be the number of subjects randomized in each treatment. For overall, the percentages will be based on the overall number of subjects in the ITT population.

The summaries will be performed on the Screened and ITT set.

All available information will be listed on the ITT Set.

#### 7.1.2. Subject disposition - cycle specific

For each cycle up to cycle 6, the number and percentage of subjects fulfilling the following will be summarized by treatment group and overall:

- Entered Cycle

- Completed treatment as per protocol
- Did not complete treatment as per protocol
- Reason for not completing treatment as per protocol (with reason: Subject Withdrew Consent, Death, Lost to follow-up, Protocol violation, Termination of the study by the sponsor, Subject becomes pregnant, Other)
- Continued to the next cycle

The summaries will be performed on the ITT set.

All available information will be listed on the ITT Set.

#### 7.1.3. Study population

The Number and percentage of subjects fulfilling the following will be summarized by treatment group and overall:

- Subjects in the ITT set
- Subject in ITT set randomized on stratum:
  - o Newly Diagnosed - Male - Non Smoker - Stage IIIB
  - o Newly Diagnosed - Male - Non Smoker - Stage IV
  - o Newly Diagnosed - Male - Smoker - Stage IIIB
  - o Newly Diagnosed - Male - Smoker -Stage IV
  - o Newly Diagnosed - Female - Non Smoker - Stage IIIB
  - o Newly Diagnosed - Female - Non Smoker - Stage IV
  - o Newly Diagnosed - Female - Smoker - Stage IIIB
  - o Newly Diagnosed - Female - Smoker -Stage IV
  - o Recurrent Disease - Male - Non Smoker - Stage IIIB
  - o Recurrent Disease - Male - Non Smoker - Stage IV
  - o Recurrent Disease - Male - Smoker - Stage IIIB
  - o Recurrent Disease - Male - Smoker -Stage IV
  - o Recurrent Disease - Female - Non Smoker - Stage IIIB
  - o Recurrent Disease - Female - Non Smoker - Stage IV
  - o Recurrent Disease - Female - Smoker - Stage IIIB
  - o Recurrent Disease - Female - Smoker -Stage IV
- Subjects in the mITT set
- Reason for exclusion of ITT subjects from mITT (not treated with IMP, did not have measurable disease at screening as determined by central radiological review)
- Subjects in the PPS set
- Reason for exclusion of ITT subjects from PPS (did not complete cycle 6 assessment, have at least 1 major protocol deviation, other)

- Subjects in the SAF set

The summaries will be performed on the ITT set.

All available information will be listed on the ITT Set.

#### 7.1.4. Protocol deviations

The Number and percentage of subjects fulfilling the following will be summarized by treatment group and overall:

- Subjects experiencing at least one major deviation
- Subjects experiencing at least one major deviation coded as:
  - o Concomitant Medications
  - o Dosing
  - o Enrollment Criteria
  - o Informed Consent
  - o Laboratory
  - o Non-Compliance
  - o Regulatory
  - o Visit Schedule
  - o Visit/Procedure Required

In an additional table, the number and percentage of major deviations will be summarized (here 100% will be the total number of major deviations). The following will be summarized by treatment group and overall:

- Total number of major deviations
- Total number of major deviations coded as:
  - o Randomization criteria deviations
  - o Inclusion/Exclusion criteria deviations.
  - o Inadequate compliance with study drug.
  - o Prohibited medications taken.
  - o Significant deviations from the study drug administration schedule.
  - o No valid evaluation of the primary efficacy endpoint.
  - o Other protocol deviations that could affect subjects' efficacy outcomes.

The summaries will be performed on the ITT set.

A listing will be produced containing the following information:



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- Date
- Minor or Major deviation
- Category of deviation
- Description of deviation

The listing will be presented for the ITT Set.

## 7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The following information will be summarized by treatment group and overall:

- Gender (%)
- Females of child bearing potential
- Age
- Categorical age as < 65 years and ≥ 65 years
- Race (including subjects with race not reported)
- Smoking status
- Pack per Year
- Duration of smoking
- Stratification Smoking status (as smoker or non -smoker)
- DSMB Stratification Smoking status (as smoker or non -smoker)
- Height
- Weight
- BSA

Summaries will be performed on the ITT, PPS and on SAF sets.

A listing will be produced containing the same information as the summary.

## 7.3. MEDICAL HISTORY AND CONCOMITANT DISEASES

### 7.3.1. NSCLC history

The following information will be summarized by treatment group and overall:

The following information will be summarized:

- NSCLC time from first diagnosis (in weeks)
- NSCLC diagnosis type (Newly diagnosed vs Recurrent disease)
- NSCLC stage at screening.

Summaries will be performed on the ITT set.

All available information on NSCLC medical history will be listed on the ITT set.

#### **7.3.2. Non NSCLC Medical History**

At the end of the study, medical history will be coded using System Organ Class (SOC) and Preferred Term (PT).

The following information will be summarized by treatment group and overall:

Previous medical history - SOC and PT  
Summaries will be produced on the ITT set.

Non NSCLC medical history summaries will be sorted by frequency (descending order based on overall totals) by SOC and PT.

All available information on Non NSCLC medical history will be listed on the ITT set.

#### **7.4. OTHER BASELINE CHARACTERISTICS**

No other baseline characteristics will be evaluated

#### **7.5. MEDICATION AND OTHER PROCEDURES**

Prior NSCLC and prior non-NSCLC/concomitant medication are reported on two separate CRFs. Rules for discriminating prior/concomitant medications are defined in section 6.2.18.

Medication will be coded using WHO-DD version September 2017 using Anatomical Therapeutic Chemical (ATC) Classification Level 2 and Level 3 plus any applicable sorting (e.g. type of therapy and/or setting). The latest available version available at the end of study will be used.

##### **7.5.1. Prior NSCLC systemic therapy**

The following information will be summarized by treatment group and overall:

- Type of therapy, Setting, ATC Level 2 and 3.

Summaries will be produced on the ITT set.

Sorting will be done by Type of Therapy, Setting, ATC level 2 (descending frequency based on overall totals) and level 3 (descending frequency based on overall totals)

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All available information will be listed on the ITT set.

#### **7.5.2. Prior/Concomitant Medication**

The following information will be summarized by treatment group and overall:

- ATC Level 2, ATC Level 3 and Preferred Term for prior medication
- ATC Level 2, ATC Level 3 and Preferred Term for concomitant medication

Summaries will be produced on the ITT set.

Sorting will be done by Prior/Concomitant Medication, ATC level 2 (descending frequency based on overall totals) and level 3 (descending frequency based on overall totals)

All available information will be listed on the ITT set.

#### **7.5.3. Prior NSCLC radiotherapy**

The following information will be summarized by treatment group and overall:

- Reason, Site of lesion, Setting

Summaries will be produced on the ITT set.

Sorting will be done by Reason, Site of lesion (descending frequency based on overall totals), Setting (descending frequency based on overall totals)

All available information will be listed on the ITT set.

#### **7.5.4. Prior NSCLC surgery**

The following information will be summarized by treatment group and overall:

- Type of surgery, Site of lesion, Setting.

Summaries will be produced on the ITT set.

Sorting will be done by Type of surgery, Site of lesion (descending frequency based on overall totals), Setting (descending frequency based on overall totals)

All available information will be listed on the ITT set.

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**7.5.5. Non NSCLC surgical history**

All available information will be listed on the ITT set.

**7.5.6. Other prior/concomitant procedures**

All available information will be listed on the ITT set.



## 8. EFFICACY

### 8.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

#### 8.1.1. Main analysis - FDA

Per the US FDA recommendation the equivalence analysis will be based on the RR (Type II meeting of 30<sup>th</sup> June 2017 and 31<sup>st</sup> July 2017 follow-up letter). Further to this, based on FDA recommendation (Type II meeting of 4<sup>th</sup> October 2018), the equivalence margin [0.73, 1.36] will be used to ascertain clinical equivalence of the primary efficacy endpoint.

The statistical hypotheses associated with the primary analysis of ORR at Week 18 using risk ratio is:

- $H_0: (ORR_{MB02} / ORR_{Avastin} \leq 0.73) \text{ or } (ORR_{MB02} / ORR_{Avastin} \geq 1.36)$
- $H_1: 0.73 < (ORR_{MB02} / ORR_{Avastin}) < 1.36,$

where  $ORR_{MB02}$  and  $ORR_{Avastin}$  are the ORRs for MB02 and Avastin®, respectively.

The ORR estimate will be adjusted for the randomization strata sex (male/female), smoking status (smoker/nonsmoker), disease diagnosis (newly diagnosed/recurrent disease) and disease stage (Stage IIIB/Stage IV) using the Cochran- Mantel-Haenszel estimate of the RR and corresponding 2-sided 90% CI. The primary analysis will be conducted in the ITT, mITT and PP populations. For additional equivalence criteria on the primary endpoint a 2-sided 95% CI for RR will also be provided in the ITT, mITT and PP populations.

The Farrington-Manning method will be used for estimating confidence intervals (CIs).

The Cochran Q test will be used to evaluate strata homogeneity. In case of heterogeneity, the plausible non homogeneous strata will be removed from analysis and a new estimate produced using the homogeneous strata. The Cochran Q test will be rerun to satisfy this assumption. The Breslow Day test will be used for checking the assumption on homogeneity of Odds Ratio. It is recognized that a Relative Risk is estimated, nevertheless this test could be used as a proxy for homogeneity of Relative Risk. However only the Q test will be used to formally evaluate the homogeneity assumption. At least two sets of results (each including the RR estimate and the two-sided 90% CI) will be presented (for the homogeneous strata and for each single non homogeneous stratum).

In case the estimation is not produced due to low prevalence of stratum (e.g. too few subjects) a similar strategy will be used (i.e. remove the stratum/a with low prevalence and compute the estimates on the remaining).

### 8.1.2. Main analysis - EMA

The EMA requested that the difference in ORRs should be used as the primary efficacy analysis (Follow-up Scientific Advice - 22<sup>nd</sup> June 2017). Hence, this additional analysis will be performed and included as part of the primary efficacy analysis.

The statistical hypotheses associated with the primary analysis of ORR at Week 18 using risk difference is:

- $H_0: (ORR_{MB02} - ORR_{Avastin} \leq -12\%) \text{ or } (ORR_{MB02} - ORR_{Avastin} \geq +12\%)$
- $H_1: -12\% < (ORR_{MB02} - ORR_{Avastin}) < +12\%$ ,

where  $ORR_{MB02}$  and  $ORR_{Avastin}$  are the ORRs for MB02 and Avastin®, respectively.

The ORR estimate will be adjusted for the randomization strata sex (male/female), smoking status (smoker/nonsmoker), disease diagnosis (newly diagnosed/recurrent disease) and stage (Stage IIIB/Stage IV) using the Cochran- Mantel-Haenszel estimate of the RD and corresponding 2-sided 90% CI. This primary analysis will be conducted in the ITT, mITT and PP populations. For additional equivalence criteria on the primary endpoint, as an exploratory analysis, a 2-sided 95% CI for RD will also be provided in the ITT, mITT and PP populations.

The Newcombe method will be used for estimating CIs.

The Cochran Q test will be used to evaluate strata homogeneity. In case of heterogeneity, the plausible non homogeneous strata will be removed from analysis and a new estimate produced using the homogeneous strata. The Cochran Q test will be rerun to satisfy this assumption. At least two sets of results (each including the RD estimate and the 90% CI) will be presented (for the homogeneous strata and for each single non homogeneous stratum).

In case the estimation is not produced due to low prevalence of stratum (e.g. too few subjects) a similar strategy will be used (i.e. remove the stratum/a with low prevalence and compute the estimates on the remaining).

### 8.1.3. Main analysis - PMDA

Per the PMDA requirements the statistical hypotheses associated with the primary analysis of ORR at Week 18 using risk ratio is:

- $H_0: (ORR_{MB02} / ORR_{Avastin} \leq 0.73) \text{ or } (ORR_{MB02} / ORR_{Avastin} \geq 1.36)$
- $H_1: 0.73 < (ORR_{MB02} / ORR_{Avastin}) < 1.36$ ,

where  $ORR_{MB02}$  and  $ORR_{Avastin}$  are the ORRs for MB02 and Avastin®, respectively.

The ORR estimate will be adjusted for the randomization strata sex (male/female), smoking status (smoker/nonsmoker), disease diagnosis (newly diagnosed/recurrent disease) and disease stage (Stage IIIB/Stage IV) using the Cochran- Mantel-Haenszel estimate of the RR and corresponding 2-sided 95% CI. The primary analysis will be conducted in the ITT, mITT and PP populations.

#### **8.1.4. Main analysis - output**

The following information will be summarized by treatment group and overall:

- Objective Response and ORR

Within the same table the following will be reported:

- Estimate of RR of ORR and two-sided 90% and 95% CIs
- Estimate of RD of ORR and two-sided 90% and 95% CIs
- Estimate of RR of ORR and two-sided 90% and 95% CIs (only if non homogenous/low prevalence strata)
- Estimate of RD of ORR and two-sided 90% and 95% CIs (only if non homogenous/low prevalence strata)
- Cochran Q p value - RD
- Cochran Q p value - RR
- Breslow Day p value

Summaries will be produced on the ITT, mITT and PP sets.

All available information will be listed on the ITT set.

##### **8.1.4.1. Supportive analyses**

##### **8.1.4.2. Investigator Assessment**

In addition to ORR being assessed via an independent radiology review committee (IRC), ORR will also be assessed based on the investigators tumor assessment at week 18, as a supportive analysis.

##### **8.1.4.3. Within strata analysis**

RR and RD estimate and the two-sided 90% CIs of ORR (as described in sections 8.1.1 and 8.1.2) will be restricted within each stratification factor on the ITT set (i.e. 16 analyses in total).

#### **8.1.4.4. Unadjusted analysis**

In addition to the main FDA analysis in section 8.1.1 and the main EMA analysis in section 8.1.2 an unadjusted analysis (without any strata) will also be carried out.

#### **8.1.4.5. DSMB smoker definition analysis**

In addition to the main FDA analysis in section 8.1.1 and the main EMA analysis in section 8.1.2 an analysis using the DSMB smoker definition will also be carried out.

#### **8.1.5. Within strata analysis - output**

The following information will be summarized for each RR and RD related analysis:  
- estimate and two-sided 90% CIs of within strata analysis (16 estimates/CIs)

Summaries will be produced on the ITT set.

Forest plots containing the information summarized will be produced on the ITT set.  
In addition they will contain the following:

- estimate and two-sided 90% CI of main analysis

### **8.2. SECONDARY EFFICACY ENDPOINT(S) AND ANALYSES**

#### **8.2.1. Progression Free Survival**

This exploratory endpoint is defined in section 4.3.1

The Cox proportional hazards model will be used to estimate the Hazard Ratio and its 90% CI of MB02 compared with Avastin®.

The main Cox proportional hazards model will include treatment group (reference: Avastin®), with sex, smoking status, disease diagnosis, and disease stage as covariates. The proportional hazard assumption will be evaluated on all covariates (ie, treatment and stratification factors) by graphical inspection of the Schoenfeld residuals and by Grambsch and Therneau test as well.

In case the non-proportional hazards assumption does not hold for a factor, the cox regression will be performed stratifying for that factor.



In case the proportional hazards assumption does not hold for the treatment group the area under the curve for the PFS (i.e. the Restricted Mean Survival Time [RMST]) estimated by the KM estimator for each treatment up to 52 weeks will be computed and the difference (reference: Avastin®) will be reported. Standard Error will be computed using Jackknife estimation (Royston, 2011).

### 8.2.2. Overall Survival

This exploratory endpoint is defined in section 4.3.2. The same approach described in 8.2.1 will be used.

### 8.2.3. Secondary Efficacy Endpoint - output

The following information will be summarized by treatment group and overall:

- Estimate and two-sided 90% CI of the median PFS (from the Kaplan Meier estimator)
- Estimate and two-sided 90% CI of the median OS (from the Kaplan Meier estimator)

Within the same table the following will be reported:

- Estimate and two-sided 90% CI of the Hazard Ratio (outcome PFS) from Conventional/Stratified Cox model (if PH assumption holds for at least the treatment group)
- Estimate and two-sided 90% CI of the difference in RMST (outcome PFS) (only if PH assumption does not hold for the treatment group)
- Grambsch and Therneau test p-value from Cox Model - PFS
- Estimate and two-sided 90% CI of the Hazard Ratio (outcome OS) from Conventional/Stratified Cox model (if PH assumption holds for at least the treatment group)
- Estimate and two-sided 90% CI of the difference in RMST (outcome OS) (only if PH assumption does not hold for the treatment group)
- Grambsch and Therneau test p-value from Cox Model - OS

Summaries will be produced on the ITT, mITT and PP sets.

A graph containing the KM estimates of PFS will be produced on the ITT, mITT and PP sets.

A graph containing the KM estimates of OS will be produced on the ITT, mITT and PP set.

A graph containing the Schoenfeld residuals by each covariate will be produced (this will be produced internally and will not displayed as an official output as it is a supportive graph for checking model assumption). This will be repeated for OS.

Information will be listed on the ITT set.

#### **8.2.4. Duration of Overall Response**

This exploratory endpoint is defined in section 4.3.3. The same approach described in section 4.3.3 will be used at week 52.

#### **8.2.5. Observation Time**

This exploratory endpoint is defined in section 4.3.4. The same approach described in 8.2.1 will be used at week 52.

#### **8.2.6. Time to Overall Response**

This exploratory endpoint is defined in section 4.3.2. The same approach described in 8.2.1 will be used at week 52.

### **8.3. LESION ASSESSMENTS**

All information (target, non-target and new lesions) will be presented for both CRF data and Bioclinica data and listed on the ITT set.

## 9. SAFETY

### 9.1. EXTENT OF EXPOSURE

Exposure will be presented both for the primary analysis endpoint at week 18 and also for the week 52 analysis upon the completion of the study.

#### 9.1.1. MB02/AVASTIN®

The following information will be summarized by treatment group and overall:

- Duration of exposure (days)
- Subjects with at least one intended dose of 15 mg/Kg
- Number of cycles per subject
- Cycle categories: 1-2 cycles, 3-4 cycles, 5-6 cycles, more than 6 cycles
- Actual dose administered (mg)
- Total doses administered
- Subjects with a dose modified at least once
- Total doses modified (among the administered)
- Duration of infusion (minutes) (among the administered doses)
- Duration of infusion (minutes) categories (among the administered doses):  
duration < 30 minutes, 30 minutes ≤ duration < 60 minutes, 60 minutes ≤ duration < 90 minutes, duration ≥ 90 minutes
- Specific reason for dose modified
- Subject with a dose delayed at least once
- Total doses delayed (among the administered)
- Specific reason for dose delayed
- Subject with a dose stopped/interrupted at least once
- Total doses stopped/interrupted (among the administered)
- Specific reason for dose stopped/interrupted
- Total doses restarted (among the stopped/interrupted)
- Total duration of infusion interruption

The summaries will be produced on the SAF set.

All available information will be listed on the SAF set.

#### 9.1.2. Carboplatin and Paclitaxel

For each drug, the same information as per MB02/AVASTIN® will be summarized with the following modifications:

Remove the summary on:

- Duration of infusion (minutes) categories (among the administered doses):  
duration < 30 minutes, 30 minutes ≤ duration < 60 minutes, 60 minutes ≤ duration  
< 90 minutes, duration ≥ 90 minutes

Add the summaries on:

- Carboplatin planned dose AUC (mg/mL x min) - only for Carboplatin
- Paclitaxel planned dose (mg/m<sup>2</sup>) - only for Paclitaxel

The summaries will be produced on the SAF set.

All available information will be listed on the SAF set.

## 9.2. TREATMENT COMPLIANCE

### 9.2.1. MB02/AVASTIN®

The following information will be summarized for applicable time windows (see section 6.4.1) by treatment group and overall:

- Compliance overall
- Compliance up to cycle 6, as specified in section 6.2.3
- Compliance per cycle

The summaries will be produced on the SAF set.

All available information will be listed on the SAF set.

### 9.2.2. Carboplatin and Paclitaxel

For each drug, the same information as per MB02/AVASTIN® will be summarized on the SAF set.

All available information will be listed on the SAF set.

## 9.3. ADVERSE EVENTS / ADVERSE DRUG REACTIONS

Adverse events (AEs) will be coded using MedDRA 20.1 to give a PT and a SOC term for each event. At the end of the study, AEs will be recoded applying the latest available MedDRA version available at this time point.

NCI-CTCAE version 4.03 will be used for grading intensity of the events.



Each subject may only contribute once to each incidence of a TEAE following a given treatment, regardless of the number of occurrences. The highest severity or highest relationship will be presented, as appropriate.

The causal relationship of an AE to study drug will be assessed according to the study protocol. Those considered related are those rated as: possible, probable, very likely or unknown.

An overall summary of treatment-emergent adverse events (TEAEs) will show the number and percentage of subjects (and the corresponding number of TEAEs) by treatment group and overall reporting. A TEAE is defined as those events with onset date/time at or after the first MB02/Avastin infusion.

- any TEAE
- any TEAE by grade of intensity
- any grade 3 or 4 TEAE
- any drug related TEAE (overall and by grade of intensity)
  - o TEAE related to MB02/Avastin® only
  - o TEAE related to carboplatin only
  - o TEAE related to paclitaxel only
- any grade 3 or 4 drug related TEAE
- any TEAE leading to permanent treatment discontinuation of
  - o any drug of the study treatment regimen (overall and by grade of intensity)
  - o MB02/Avastin
  - o Chemotherapy (paclitaxel or carboplatin)
- any grade 3 or 4 TEAE leading to permanent treatment discontinuation of
  - o any drug of the study treatment regimen
  - o MB02/Avastin
  - o Chemotherapy (paclitaxel or carboplatin)
- any related TEAE leading to permanent treatment discontinuation of (overall and by grade of intensity)
  - o any drug

- any related AE leading to permanent discontinuation of MB02/Avastin
  - any related AE leading to permanent discontinuation of chemotherapy
- any SAE (overall and by grade of intensity)
- any SAE (overall and by grade of intensity) related to study treatment
  - any drug of the study treatment regimen
  - MB02/Avastin
  - Chemotherapy (paclitaxel or carboplatin)
- any fatal TEAE
- any fatal TEAE related to study treatment
  - any drug of the study treatment regimen
  - MB02/Avastin
  - Chemotherapy (paclitaxel or carboplatin)
- any TEAE leading to dose delay of IP
- any TEAE leading to dose delay of any component of chemotherapy
- any TEAE leading to dose reduction of any component of chemotherapy

The summaries will be produced on the SAF set.

An AE summary displaying the number of subjects who experienced TEAEs by SOC and PT by treatment group and overall will be presented for the following items:

- any TEAE
- any fatal TEAE
- any SAE
- any related SAE
- any MB02/Avastin related SAE
- any chemotherapy (paclitaxel or carboplatin) related SAE
- any related TEAE, by grade of intensity and overall
- any MB02/Avastin related TEAE, by grade of intensity and overall
- any chemotherapy (paclitaxel or carboplatin) related TEAE, by grade of intensity and overall
- any TEAE leading to permanent discontinuation of the study treatment
- any related TEAE leading to permanent discontinuation of the study treatment
- any MB02/Avastin related TEAE leading to permanent discontinuation of the study treatment

These summaries will be sorted by SOC (descending frequency based on overall totals) and PT (descending frequency based on overall totals).

The summaries will be produced on the SAF set.

All information will be listed on the SAF set.

The listings will also be created for

- any fatal TEAE
- any SAE
- any TEAE leading to permanent discontinuation of the study treatment
- any TEAE related to MB02/Avastin
- any TEAE related to carboplatin and/or paclitaxel
- any grade 3-4 TEAE

The listings will be produced on the SAF set.

#### 9.4. LABORATORY EVALUATIONS

Laboratory evaluation includes hematology, clinical chemistry, coagulation, urinalysis, (including 24 hour urine), pregnancy test and Immunogenicity. These will be performed at a central laboratory.

Immunogenicity is not covered by SAP and analyses will be performed by an external provider.

Laboratory evaluations where appropriate (excluding pregnancy) will be graded according to NCI-CTCAE version 4.03 to allow for comparison of AEs and laboratory parameters.

For each category (hematology, coagulation, clinical chemistry, urinalysis) the following information will be summarized for screening and applicable time windows (see section 6.4.1) by treatment group and overall:

- Actual Value of the parameter
- Change from baseline of the parameter

Definition of baseline is given within section 6.2.1.  
Summaries will be produced on the SAF set.

For each category, a Grade shift table from baseline to worst grade (high and low grade classification) will be produced by treatment group and overall.

For each category, a Grade shift table from baseline to each visit windows will be produced by treatment group and overall.

Summaries will be produced on the SAF set.

For each category, all available information will be listed on the SAF set.

The same listings will be repeated on grading “any grade 3 or 4”

A listing on pregnancy on the SAF set will be produced

A listing on virology on the screened set will be produced.

### **9.5. VITAL SIGNS**

The following information will be summarized for screening and applicable time windows (see section 6.4.1) by treatment group and overall:

- Actual Value of the parameter
- Change from baseline of the parameter

Definition of baseline is given within section 6.2.1.

Summary will be produced on the SAF set.

All available information will be listed on the SAF set.

### **9.6. 12-LEAD ELECTROCARDIOGRAM (ECG)**

For ECG, the following information will be summarized for screening and applicable time windows (see section 6.4.1) by treatment group and overall:

- Actual Value of the parameter
- Change from baseline of the parameter

Definition of baseline is given within section 6.2.1.

Summary will be produced on the SAF set.

A Grade shift table from baseline to worst evaluation will be produced by treatment group and overall. Evaluations will be Normal or Abnormal. Abnormal values will be further classified with respect to clinical relevance: not clinically significant (NCS) or clinically significant (CS). Abnormal is worse than normal and CS is worse than NCS.

A Grade shift table from baseline to each visit windows will be produced by treatment group and overall.

Summaries will be produced on the SAF set.

All available information will be listed on the SAF set.



## **9.7. PHYSICAL EXAMINATION**

A Grade shift table from baseline to worst evaluation will be produced for each body system by treatment group and overall. Evaluations will be Normal or Abnormal. Abnormal values will be further classified with respect to clinical relevance: not clinically significant (NCS) or clinically significant (CS). Abnormal is worse than normal and CS is worse than NCS.

Summaries will be produced on the SAF set.

All available information will be listed on the SAF set.

## **9.8. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS**

For ECOG performance status, the following information will be summarized for screening and applicable time windows (see section 6.4.1) by treatment group and overall:

- Actual Value of ECOG
- Change from baseline of ECOG

Definition of baseline is given within section 6.2.1.  
Summary will be produced on the SAF set.

All available information will be listed on the SAF set.

## **9.9. INITIATION OF NEW TREATMENT**

All available information will be listed on the SAF set.

## **9.10. LEFT VENTRICULAR EJECTION FRACTION**

The following information will be summarized for baseline and EOT by treatment group and overall:

- Left ventricular Ejection Fraction (%)

Summary will be produced on the SAF set.

All available information will be listed on the SAF set.

[REDACTED]

Statistical Analysis Plan -  
text

mAbxience Protocol MB02-C02-17

[REDACTED]

Version 2.0

#### 9.11. DEATHS

All available information will be listed in 16.2.7.2 (fatal TEAEs) on the SAF set.

## 10. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

The following additions have been made to the statistical analysis plan compared to the study protocol.

- Derivation and analysis of RR and RD estimates based on the investigators tumor assessments at week 18, as a supportive analysis.
- Derivation and analysis of duration of overall response (measured from the time when the measurement criteria are first met for CR/PR until the first date that progressive disease is objectively documented).
- Derivation and analysis of observation time (measured from the time of randomization to the date of final follow-up or death).
- Derivation and analysis of time to overall response (measured from the time of randomization to the date of first objective tumor response (CR or PR)).
- The addition of a DSMB definition of smokers and non-smokers.
- The addition of an unadjusted analysis (without any strata).
- A change in the week 18 visit window to -7/+14 days, due to some subjects having small cumulative delays in treatment administration.

## 11. REFERENCE LIST

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